GENERAL GYNECOLOGY

Regression, relapse, and live birth rates with fertility-sparing therapy for endometrial cancer and atypical complex endometrial hyperplasia: a systematic review and metaanalysis

Ioannis D. Gallos, MD; Jason Yap, MBChB; Madhurima Rajkhowa, MD; David M. Luesley, MD; Arri Coomarasamy, MD; Janesh K. Gupta, MD

OBJECTIVE: The objective of the study was to evaluate the regression, relapse, and live birth rates of early-stage endometrial cancer (EC) and atypical complex hyperplasia (ACH) with fertility-sparing treatment.

STUDY DESIGN: This was a metaanalysis of the proportions from observational studies with a random-effects model and a meta-regression to explore for heterogeneity.

RESULTS: Thirty-four observational studies, evaluating the regression, relapse, and live birth rates of early-stage EC (408 women) and ACH (151 women) with fertility-sparing treatment. Fertility-sparing treatment for EC achieved a pooled regression rate of 76.2%, a relapse rate of 40.6%, and a live birth rate of 28%. For ACH the pooled regression rate was 85.6%, a relapse rate of 26%, and a live birth rate of 26.3%. Twenty women were diagnosed with ovarian cancer (concurrent or metastatic) during follow-up (3.6%) and 10 progressed to higher than stage I EC (1.9%) from which 2 women died.

CONCLUSION: Fertility-sparing treatment of EC and ACH is feasible and selected women can satisfy their reproductive wishes.

Key words: atypical complex hyperplasia, endometrial cancer, fertility-sparing treatment, live births, progestogens

Cite this article as: Gallos ID, Yap J, Rajkhowa M, et al. Regression, relapse, and live birth rates with fertility-sparing therapy for endometrial cancer and atypical complex endometrial hyperplasia: a systematic review and metaanalysis. Am J Obstet Gynecol 2012;207;266.e1-12.

In 2007, 7536 women in the United Kingdom were diagnosed with endometrial cancer (EC) and 239 of these women were younger than 45 years old (3.2%).[1] Often these women have strong fertility desires because anovulatory infertility is strongly associated with the development of EC and atypical complex hyperplasia (ACH).[2] It is known that these women are usually diagnosed with early clinical stage, well-differentiated EC, which carries a good prognosis. Traditionally, it is recommended that these women undergo a staging abdominal hysterectomy. However, multiple studies suggest that in selected women with early clinical stage disease, this can be managed with fertility-sparing hormonal therapy.

★ EDITORS' CHOICE ★

The use of progestogens can induce endometrial regression and prevent the progression of the disease. Oral progestogens are used to treat EC and ACH, but more recently, the levonorgestrel-releasing intrauterine system (LNG-IUS; Mirena, Bayer, Berkshire, UK) has also been used successfully to treat ACH.[3] These options are also popular among clinicians for women who decline hysterectomy.[4] Yet there is significant uncertainty about the efficacy of these therapies from observational studies with small sample sizes, which makes it difficult to counsel the women accordingly. To ascertain the efficacy of these therapies, we conducted a systematic review of observational studies evaluating the regression, relapse, and live birth rates for the treatment of EC and ACH, and we performed a metaanalysis of their treatment effects.

Materials and Methods

Identification of literature

The population of interest in this systematic review was women with early clinical stage (International Federation of Gynecology and Obstetrics stage I) EC or ACH, the intervention was fertility-sparing therapies, and the outcome was evidence of disease regression, relapse, and live births. The following electronic databases were searched: MEDLINE (1950 to September 2011), EMBASE (1980 to September 2011), Cochrane Central Register of Controlled Trials and Web of Science conference proceedings

From the Academic Unit of Obstetrics and Gynaecology, Birmingham Women's Hospital (Drs Gallos, Rajkhowa, Coomarasamy, and Gupta), and the Pan-Birmingham Gynaecological Cancer Centre, City Hospital (Drs Yap and Luesley), Birmingham, England, United Kingdom.

Received April 20, 2012; revised May 26, 2012; accepted Aug. 7, 2012.

This study and I.D.G. were supported through a Wellbeing of Women entry-level scholarship (ELS022).

The authors report no conflict of interest.

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0002-9378/free

http://dx.doi.org/10.1016/j.ajog.2012.08.011

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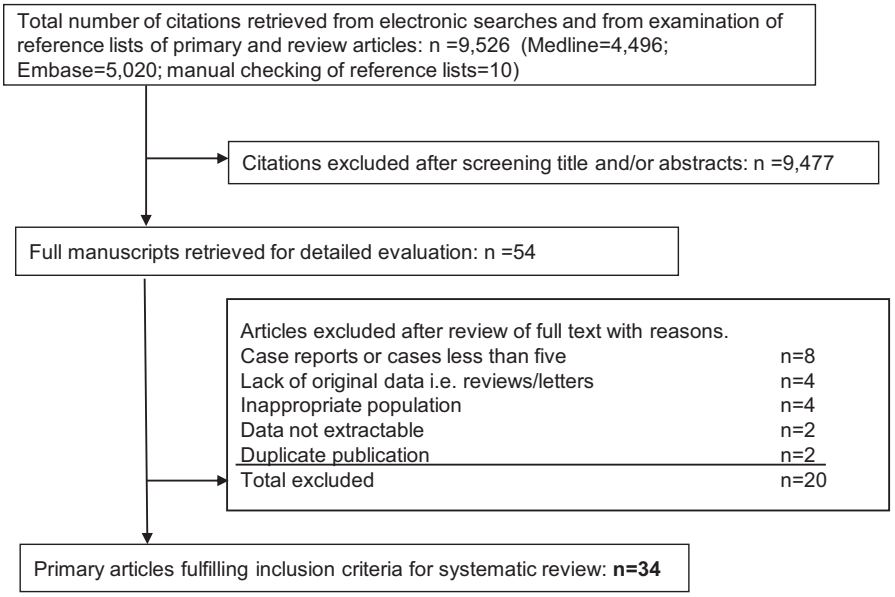
FIGURE 1
Study selection process



Gallos. Fertility-sparing therapy for endometrial cancer. Am J Obstet Gynecol 2012.

(ISI Proceedings, 1990 to September 2011).

A combination of medical subject headings (MeSH) and text words were used to generate 2 subsets of citations, 1 including studies of EC ("endometr* cancer,*" "malignant endometr*") or endometrial hyperplasia ("endometr* hyperplas,*" "premalignant endometr,*" "precancer* endometr*") and the other including studies of fertility-sparing therapies such as progestogens and intrauterine devices or systems ("intrauterine devices medicated," "Levonorgestrel," "Mirena," "intrauterine progest,*" "LNG-IU,*" "progest,*" "gestag,*" "fertility-sparing therapy," "conservative therapy," "hormone* therapy").

These subsets were combined with the word "and" and limited to the words "humans and female" to generate a subset of citations. The reference lists of all known primary and review articles were examined to identify cited articles not captured by electronic searches. Language or geographical restrictions were not applied during the search or selection.

Study selection and data extraction

Studies were selected if the participants were women diagnosed histologically with early clinical stage EC or ACH, the intervention was fertility-sparing therapy, and the outcomes were histological disease regression, relapse, or live birth rates. Case reports or series with fewer than 5 cases were excluded. Studies classifying women with endometrial hyperplasia in other than the World Health Classification 1994[5] (simple, complex, and atypical) were also excluded.

Studies were selected in a 2-stage process. First, the titles and abstracts from the electronic searches were scrutinized by 2 reviewers independently (I.D.G. and J.Y.), and full manuscripts of all citations that met the predefined selection criteria were obtained. Second, final inclusion or exclusion decisions were made on the examination of the full manuscripts. In cases of duplicates, the most recent or the most complete publication was used. Any disagreements about inclusion were resolved by consensus or arbitration by a third reviewer (A.C.). Two reviewers (I.D.G. and J.Y.) completed the quality assessment. The Methodological Index for Non-Randomised Studies (MINORS), which assesses the quality of the included studies, was implemented.[6] From each study, outcome data were extracted in 2 × 2 tables by the 2 reviewers (I.D.G. and J.Y.).

Disease regression was defined as a lack of residual EC or complex hyperplasia during follow-up endometrial sampling. Disease relapse was defined EC or complex hyperplasia diagnosis during follow-up endometrial sampling following an endometrial sample that showed disease regression. Live births was defined as the birth of healthy infants during the follow-up period, and its rate was calculated as the number of women who had a birth of healthy infants divided by the number of total of women undergoing fertility-sparing therapy. We also counted the number of women who were diagnosed with concurrent or metastatic ovarian cancer or upgraded disease to higher than stage I and deaths from this disease during follow-up.

Statistical analysis

Regression, relapse, and live birth rates were extracted from each study, and we computed the log of the ratio and its corresponding standard error for each study. We performed the metaanalysis using inverse-variance weighting to calculate the random-effects summary estimates.[7] We obtained an estimate of the between-study variance with a random-effects metaanalysis. The square root of this number is the estimated SD of the underlying effects across studies.

Because we had relative measures of effect, the confidence intervals were centered on the natural logarithm of the pooled estimate and the limits exponentiated to obtain an interval on the ratio scale.[8] Forest plots were created for each outcome, showing individual study proportions with confidence intervals (CIs) and the overall DerSimmonian-Laird pooled estimate.[9] Heterogeneity of the treatment effects was assessed graphically with forest plots and statistically analyzed using the χ^2 test.[10] Exploration of the causes of heterogeneity for the live birth rate was planned according to the reproductive method, and it was assessed with the aid of meta-regression.[11] Statistical analyses were performed using Stata 8.0 (StataCorp, College Station, TX).

TABLE
Characteristics of the studies

		Study population					
			Investigations prior to treatment to rule out invasion				
Author, year	Recruitment	Women treated	Imaging	Tumor markers	Intervention or study groups	Outcomes (rates)	Follow-up (median, range in months)
Bokhman et al, 1985 (n = 19)[12]	Prospective	G1 (n = 11) or G2 (n = 8) EC	No	No	Hydroxyprogesterone 500 mg/d for at least 3 mo	Regression	n/a
Cade et al, 2010 (n = 16)[13]	Retrospective	G1 EC	MRI	No	MPA only (n = 4) 60-400 mg/d, MPA 200-400 mg/d with LNG-IUS (n = 9), or LNG-IUS (n = 3)	Regression, relapse, and live birth	27, 3–134
Duska et al, 2001 (n = 12)[14]	Retrospective	G1 EC	No	No	Progestogens at various doses	Regression, relapse, and live birth	82, 6–358
Eftekhar et al, 2009 (n = 21)[15]	Prospective	G1 EC	MRI, CT, and USD	CA125	MA 160 mg/d	Regression, relapse, and live birth	39, 5–108
Elizur et al, 2007 (n = 8)[16]	Prospective cohort study	G1 EC	MRI	CA125	MA 160 mg/d (n = 6), MPA 200 mg/d (n = 1), or 600 mg/d (n = 1) for at least 3 mo	Regression, relapse, and live birth	51, 38–75
Gotlieb et al, 2003 (n = 13)[17]	Retrospective	G1 (n = 11) or G2-3 (n = 2) EC	MRI and CT	CA125	MA 160 mg/d (n = 8), hydroxyprogesterone 8-12 g/d (n = 2), NET 5 mg/d (n = 1), MPA 200-600 mg/d (n = 2) for at least 3 mo	Regression, relapse, and live birth	35, 10–146
Hahn et al, 2009 (n = 35)[18]	Retrospective	G1 (n = 31) or G1 and focal G2 (n = 4) EC	MRI, CT, and USD	CA125	MA 160 mg/d (n = 8) or MPA 250-1500 mg/d (n = 20) or in combination (n = 7)	Regression, relapse, and live birth	23, 2–72
Han et al, 2009 (n = 10)[19]	Retrospective	G1 (n = 5) or G2 (n = 2), EC or ACH (n = 3)	MRI and USD	CA125	MA 80-160 mg/d (n = 7), MPA 20-1000 mg/d (n = 3) for at least 3 mo	Regression, relapse, and live birth	31.5, 10–133
Imai et al, 2001 (n = 14)[20]	Retrospective	Stage I G1 (n = 5) or G2 (n = 1) and stage II G1 (n = 7) or G2 (n = 1) EC	No	No	MPA 400-800 mg/d	Regression, relapse, and live birth	12.9, 7–46
Jadoul and Donnez, 2003 (n = 7)[21]	Retrospective	G1 EC (n = 5) or ACH (n = 2)	No	No	Endometrial resection followed by GnRH analogues	Regression, relapse, and live birth	40, 26–40
Kaku et al, 2001 (n = 30)[22]	Retrospective	G1 (n = 10) or G2 (n = 2), EC or ACH (n = 18)	MRI, CT, and USD	No	MPA 200-800 mg/d for EC (n = 12) and 100-600 mg/d for ACH (n = 18) for 3-6 mo	Regression, relapse, and live birth	38.7, 17–84
Kim et al, 1997 (n = 7)[23]	Retrospective	G1 EC	No	No	MA 160 mg/d for at least 3 mo	Regression, relapse, and live birth	11.7, 3–30
Laurelli et al, 2011 (n = 14)[24]	Prospective	Stage IA G1 EC	MRI and USD	No	Hysteroscopic resection of the tumor followed by MA 160 mg/d for 6 mo (n = 6) or LNG-IUS (52 mg/d) (n = 8) for 12 mo	Regression, relapse, and live birth	n/a
Le Digabel et al, 2006 (n = 13)[25]	Retrospective	Stage IA G1-2 (n = 3) or stage IB G2-3 (n = 2), EC or ACH (n = 8)	No	No	Progestogens at various doses (n = 6) or LHRH analogs (n = 3) or combination of the 2 (n = 2) or endometrial curettage (n = 2)	Regression, relapse, and live birth	50.5, 32–77
Lee et al, 2010 (n = 12)[26]	Prospective	ACH (n = 1), other hyperplasia (n = 11)	No	No	Progesterone-releasing IUD system (20 μg/d)	Regression and relapse	50.5, 21–82
Li et al, 2008 (n = 5)[27]	Prospective	ACH (n = 3), other hyperplasia (n = 2)	No	No	Letrozole 2.5 mg/d for 3 mo	Regression, relapse, and live birth	40.7, 2–109
Mao et al, 2010 (n = 6)[28]	Prospective	G1 EC	MRI, CT, and USD	CA125	MA 160 mg/d (n = 2), MPA 250-500 mg/d (n = 4)	Regression, relapse, and live birth	29, 4–102

Gallos. Fertility-sparing therapy for endometrial cancer. Am J Obstet Gynecol 2012.

(continued)

TABLE
Characteristics of the studies *(continued)*

		Study population					
			Investigations prior to treatment to rule out invasion				
Author, year	Recruitment	Women treated	Imaging	Tumor markers	Intervention or study groups	Outcomes (rates)	Follow-up (median, range in months)
Mazzon et al, 2010 (n = 6)[29]	Prospective	Stage IA G1 EC	MRI	CA125	Hysteroscopic resection of the tumor followed by MA 160 mg/d for 6 m	Regression, relapse, and live birth	43, 3–75
Minaguchi et al, 2007 (n = 31)[30]	Prospective	Stage IaG1 EC (n = 19) or ACH (n = 12)	MRI, CT, and USD	No	MPA 2.5-600 mg/d, mostly 400-600 mg/d for 6 mo	Regression, relapse, and live birth	55.8, 24–138
Minig et al, 2011 (n = 34)[31]	Prospective	Stage IaG1 EC (n = 14) or ACH (n = 20)	MRI and USD	CA125	LNG-IUS (20 μg/d) for 12 mo and GnRH analog (3.75 mg depot) for 6 mo	Regression, relapse, and live birth	43.5, 13–127
Montz et al, 2002 (n = 12)[32]	Prospective	Stage IaG1 EC (n = 12)	MRI and USD	No	Progesterone-releasing IUD (65 μg/d)	Regression and relapse	47.3, 18–135
Niwz et al, 2005 (n = 12)[33]	Prospective	Stage IaG1 EC	MRI and USD	CA125	MPA 400-600 mg/d for at least 6 mo	Regression, relapse, and live birth	60.2, 8–412
Otz et al, 2005 (n = 12)[34]	Retrospective	Stage IaG1 EC	MRI, CT, and USD	No	MPA 600 mg/d	Regression, relapse, and live birth	40, 9–79
Parz et al, 2012 (n = 14)[35]	Retrospective	Stage IaG1 EC	MRI	No	MPA 250-500 mg/d (n = 10) or Provera 30 mg/d (n = 2) or MA 16-240 mg/d (n = 2)	Regression, relapse, and live birth	98, 35–176
Perri et al, 2011 (n = 27)[36]	Retrospective	Stage I EC	MRI, CT, and USD	CA125	MA 160-320 mg/d (n = 21), NET 5 mg/d (n = 1), hydroxyprogesterone 2-3 g/wk (n = 2), and MPA 100-600 mg/d (n = 3)	Regression, relapse, and live birth	47.9, 25–73
Randall and Kurman, 1997 (n = 33)[37]	Retrospective	G1 EC (n = 14) or ACH (n = 19)	No	No	MPA 10-30 mg/d or MA 40-160 mg/d (n = 29), ovulation induction (n = 2), Bromocriptine (n=1), oral contraceptive (n = 1) for 3-12 mo	Regression, relapse, and live birth	69, 25–113
Signorelli et al, 2009 (n = 21)[38]	Prospective	Stage IaG1 EC (n = 11) or ACH (n = 10)	MRI, CT, and USD	CA125, CA19.9	Natural progesterone 200 mg/d, days 14-25	Regression, relapse, and live birth	11, n/a
Ushijima et al, 2007 (n = 45)[39]	Prospective	Stage IaG1 EC (n = 28) or ACH (n = 17)	MRI	CA125	MPA 600 mg/d with low-dose (81 mg) aspirin	Regression, relapse, and live birth	76.5, 21–118
Wang et al, 2002 (n = 9)[40]	Prospective	Stage IaG1 EC	MRI and USD	CA125	MA 160 mg/d and tamoxifen 30 mg/d for 6 mo	Regression, relapse, and live birth	39, 24–69
Wheeler et al, 2007 (n = 44)[41]	Retrospective	G1 EC (n = 26) or ACH (n = 18)	No	No	Oral progestogens (n = 29) or progesterone-releasing IUD (n = 15)	Regression and relapse	48.8, 14–132
Yahata et al, 2006 (n = 8)[42]	Prospective	Stage IaG1 EC	MRI and USD	No	MPA 1800 mg/d for at least 3 mo	Regression, relapse, and live birth	34.6, 7–114
Yamazawa et al, 2007 (n = 9)[43]	Prospective	Stage IaG1 EC	MRI and CT	CA125	MPA 400 mg/d for at least 6 mo	Regression, relapse, and live birth	82, 6–358
Yang et al, 2005 (n = 6)[44]	Prospective	Stage IaG1 EC	MRI, CT, and USD	No	MA 160 mg/d for at least 6 mo	Regression, relapse, and live birth	39, 5–108
Yu et al, 2006 (n = 25)[45]	Retrospective	Stage IaG1 EC (n = 8) or ACH (n = 17)	MRI, CT, and USD	CA125	MPA 250-500 mg/d for EC and 100-500 mg/d for ACH (n = 22) or MA or hydroxyprogesterone (n = 3)	Regression, relapse, and live birth	51, 38–75

ACH, atypical complex hyperplasia; *CT,* computed tomography; *EC,* endometrial cancer; *GnRH,* gonadotropin-releasing hormone; *IUD,* intrauterine device; *LHRH,* luteinizing hormone–releasing hormone; *LNG-IUS,* levonorgestrel-releasing intrauterine system; *MA,* megestrol acetate; *MPA,* medroxyprogesterone acetate; *MRI,* magnetic resonance imaging; *NET,* norethisterone; *USD,* ultrasound.

Gallos. Fertility-sparing therapy for endometrial cancer. Am J Obstet Gynecol 2012.

RESULTS

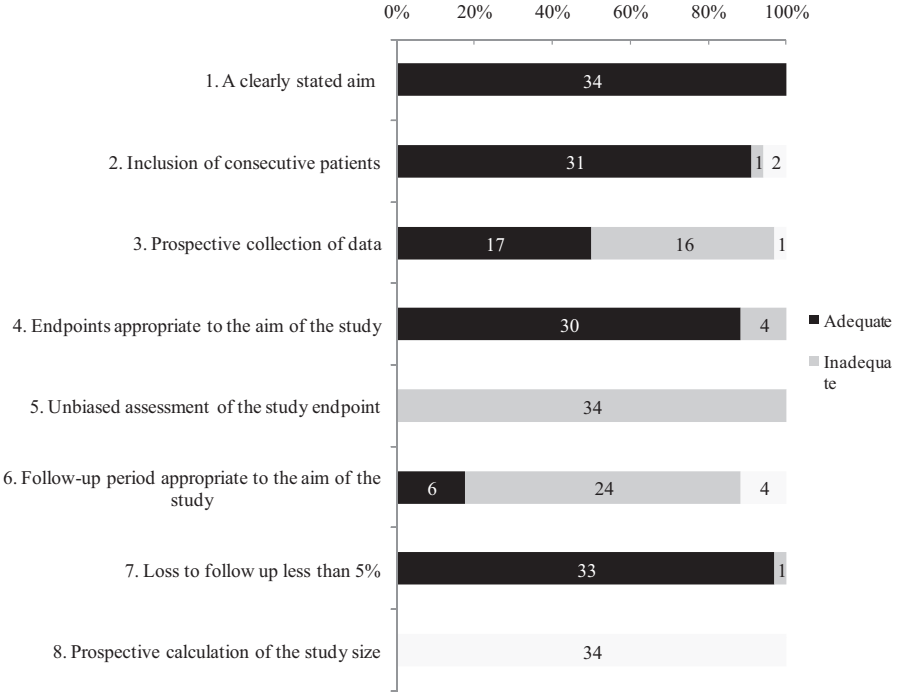
Selection, characteristics and quality of the primary studies

The electronic search strategy yielded 9516 citations, and we retrieved a further 10 citations from our manual checking of reference lists of all primary articles. Of these, 9477 citations were excluded because they did not fulfill the selection criteria. Examination of the full text of the remaining 54 manuscripts found a total of 34 primary studies,[12-45] including 559 women, of which 408 were diagnosed with EC and 151 with ACH, for inclusion in this review (Figure 1). The main characteristics of the 34 studies and the study methodological index are presented in the Table and Figure 2.

The primary studies included women with well-differentiated EC with 386 women being classified as G1 and 22 women with moderate or poor differentiation (G2 or G3). In 24 studies, the women enrolled underwent diagnostic imaging to rule out myometrial invasion or distant disease. In 11 of these 24 studies, the serum CA-125 marker was measured to also rule out concurrent ovarian malignancy.

The quality of the studies on the MINORS checklist is shown in Figure 2. More in detail, half of the studies were prospective cohorts (17 of 34) including consecutive patients (31 of 34) with adequate definition of outcomes (30 of 34). No studies had a blinded assessment of the outcomes or performed a prospective calculation of the study size. We defined appropriate follow-up to be at least 5 years, and we found that in only 6 of 34 studies, follow-up was more than 5 years.

FIGURE 2
Quality assessment of the studies



Gallos. Fertility-sparing therapy for endometrial cancer. Am J Obstet Gynecol 2012. Am J Obstet Gynecol 2012.

Regression, relapse, and live birth rates of fertility-sparing treatment for EC

Metaanalysis of the 32 studies (408 women) of women with EC managed with fertility-sparing treatment found that 301 women regressed with a pooled regression rate of 76.2% (95% CI, 68–85.3, Figure 3). The *P* value for the χ^2 test for heterogeneity was .976, indicating an insignificant variability in the regression rates between the studies. In 29 of these studies (267 women), women were followed up over time with the median ranging from 11 to 76.5 months, and the relapse rates were reported. We found that 89 women after an initial regression of the EC relapsed during follow-up, which amounts to a pooled relapse rate of 40.6% (95% CI, 33.1–49.8) without significant variability ($P = .566$, Figure 4). Metaanalysis of the 26 studies reporting pregnancy outcomes showed that from 325 women undergoing fertility-sparing treatment for EC, 75 women achieved at least 1 live birth, with a pooled live birth rate of 28% (95% CI, 21.6–36.3) with minimal heterogeneity ($P = .197$, Figure 5).

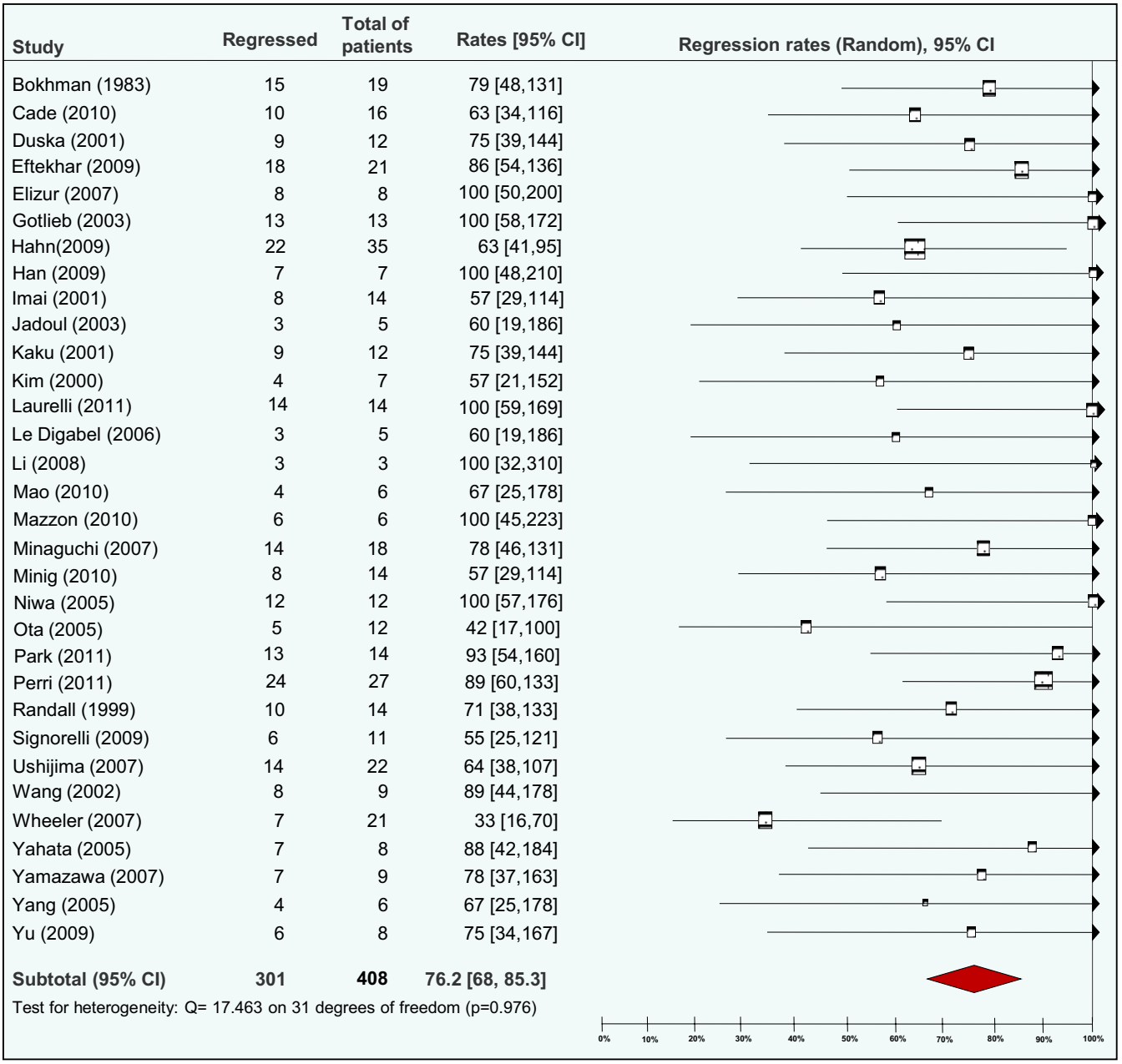
Regression, relapse, and live birth rates of fertility-sparing treatment for ACH

For ACH, metaanalysis of the 14 studies (151 women) found that 127 women regressed with a pooled regression rate of 85.6% (95% CI, 72–100%, Figure 6). The *P* value for the χ^2 test for heterogeneity was .99, indicating no variability in regression rates between the studies. In 13 of these studies (126 women), women were followed up over time with the median ranging from 11 to 76.5 months and the relapse rates were reported. We found that 27 women after an initial regression of the ACH relapsed during follow-up, which amounts to a pooled relapse rate of 26% (95% CI, 18–37.6), again without any observed variability ($P = .923$, Figure 7). For ACH, the metaanalysis of the 10 studies reporting pregnancy outcomes showed that from 126 women, 31 women achieved at least 1 live birth, with a pooled live birth rate of 26.3% (95% CI, 18.5–37.4%) with insignificant heterogeneity ($P = .877$, Figure 8).

Assisted reproduction versus spontaneous pregnancy

From the 451 women that had fertility-sparing treatment for EC or ACH, 142 had assisted reproduction treatment to achieve pregnancy and 56 of them achieved at least 1 live birth. This amounts to a 39.4% live birth rate. The remaining 309 women are presumed to have tried to spontaneously conceive and 46 women achieved at least 1 live birth, with a rate of 14.9%. This difference between assisted reproduction and spontaneous conception in achieving a live birth was statistically significant ($P = .001$) in meta-regression analysis.

FIGURE 3
Forest plot of metaanalysis of regression rates for fertility-sparing treatment of endometrial cancer



Gallos. Fertility-sparing therapy for endometrial cancer. Am J Obstet Gynecol 2012.

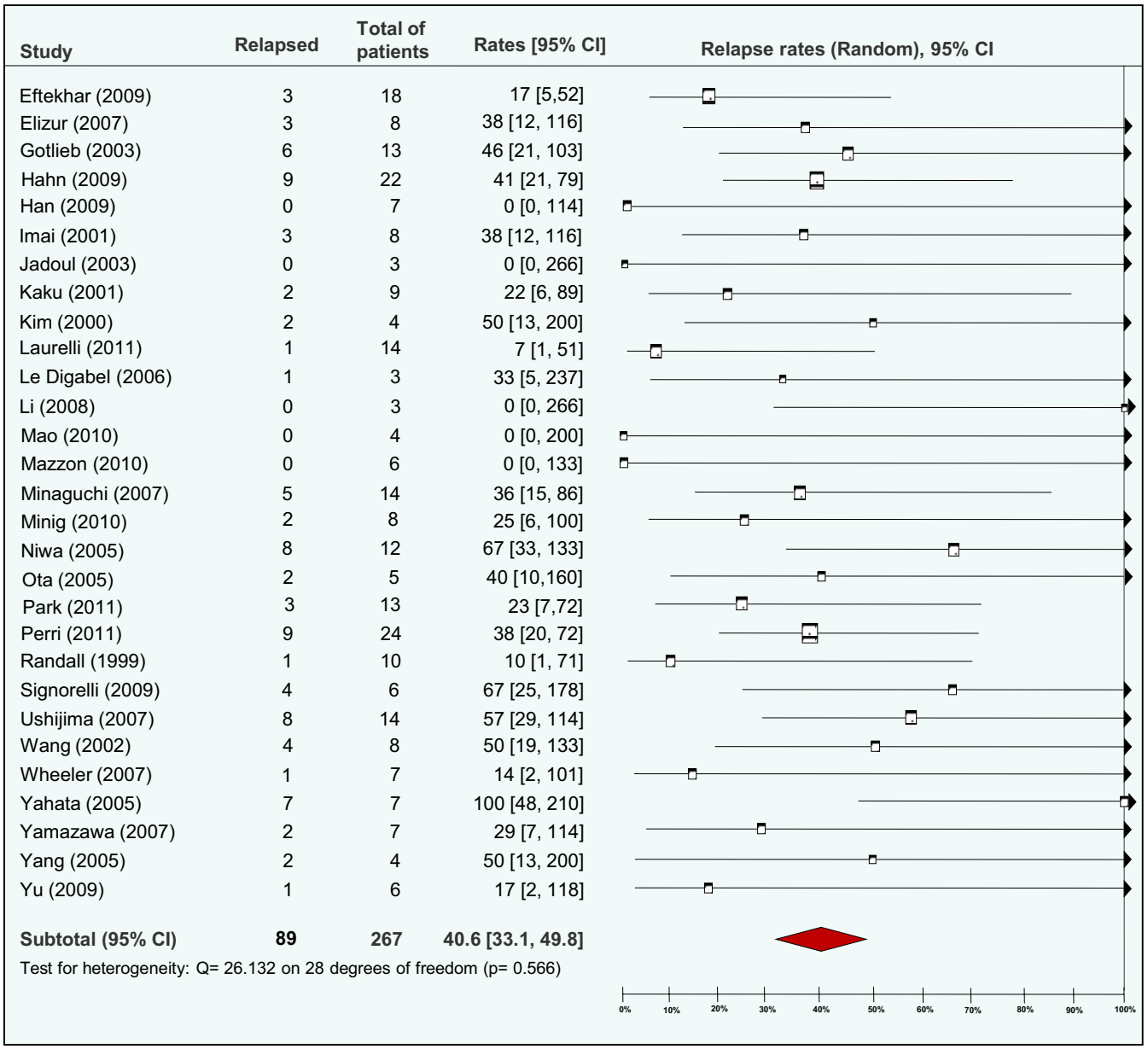
Safety of fertility-sparing treatment

There were 20 diagnoses of ovarian malignancy during follow-up (20 of 559, 3.6%), and it was not always clear from the primary studies whether they represented concurrent ovarian malignancies or metastatic ovarian involvement from the endometrial primary neoplasm. The type of ovarian cancer and staging was poorly reported, but 10 women were diagnosed with endometrioid adenocarcinoma of the ovary (10 of 559, 1.8%).

The preoperative imaging or tumor marker investigations did not appear to reduce this incidence because in 11 studies that carried out these investigations, ovarian malignancy was diagnosed during follow-up in 8 women (8 of 200, 4%) compared with 13 studies in which only imaging was used, and there were 5 ovarian malignancies diagnosed (5 of 217, 2.3%), and in 10 studies with no such investigations, there were 7 ovarian malignancies diagnosed (7 of 142, 4.9%).

There were also 10 women (10 of 559, 1.8%) diagnosed with stage II EC or higher after failing treatment. In 1 case there was a distal lymphatic metastasis involving the obturator lymphatic node.[22] There were 2 deaths from fertility-sparing treatment for

FIGURE 4
Forest plot of metaanalysis of relapse rates for fertility-sparing treatment of endometrial cancer



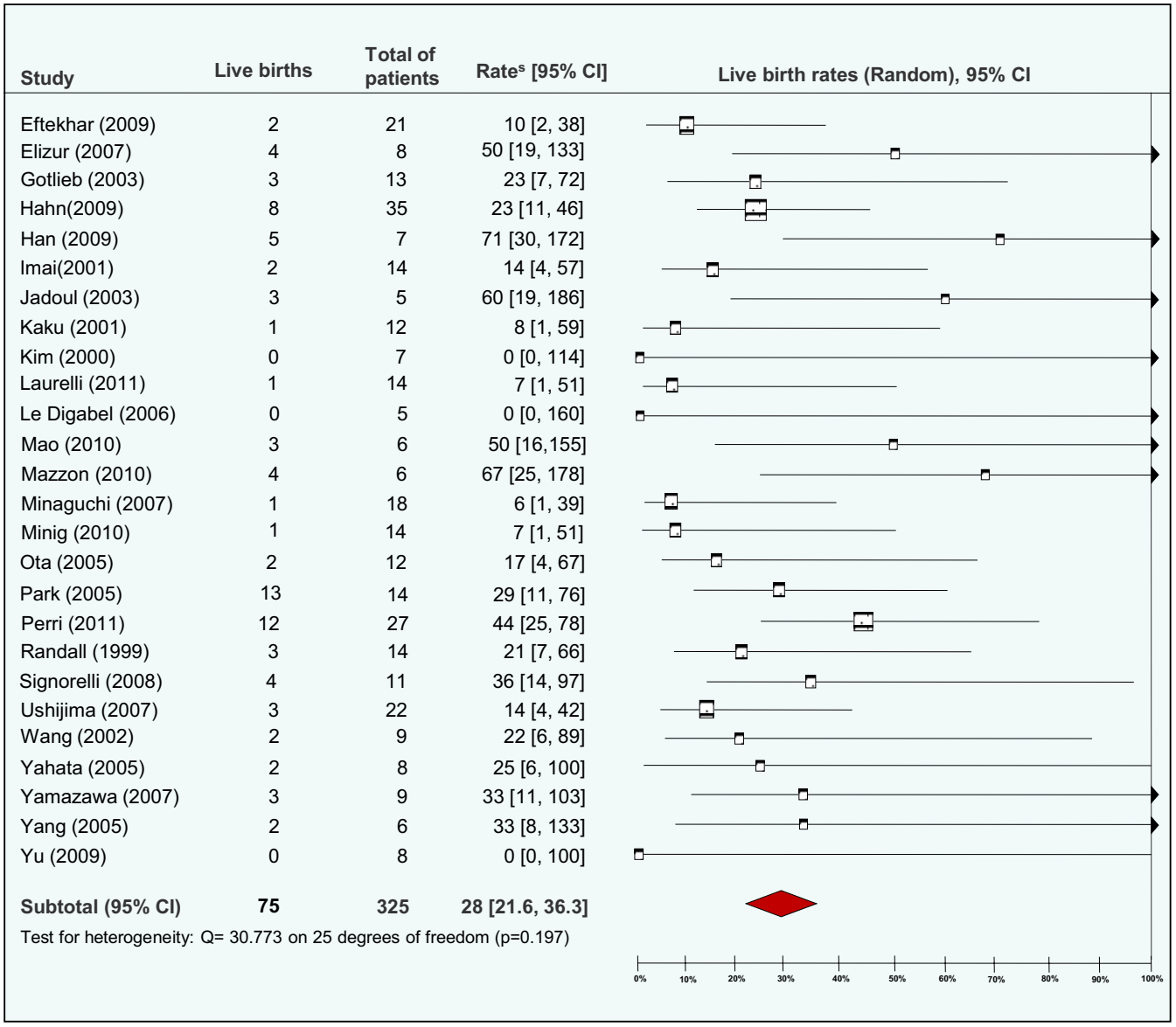
Gallos. Fertility-sparing therapy for endometrial cancer. Am J Obstet Gynecol 2012.

EC (2 of 559, 0.36%), 1 from a diagnosis of a synchronous endometrial, ovarian, and peritoneal malignancy[39] and 1 from an ovarian malignancy on a patient who on recurrence underwent only total hysterectomy without salpingo-oophorectomy because she did not want to have menopausal symptoms.[34]

COMMENT

This metaanalysis, which included 408 women with EC and 151 with ACH, found that the regression rates with fertility-sparing treatment are very encouraging (76% for EC and 86% for ACH). An additional encouraging proportion of women choosing this treatment for preserving their fertility managed to achieve live births (28% of women with EC and 26% of women with ACH). Women choosing assisted reproductive treatment had significantly better results, regardless of the initial diagnosis. However, the relapse rates during follow-up are worrying (41% for EC and 26% for ACH). The incidence of ovarian malignancies in 20 women during follow-up is also worrying (3.6%), and the preoperative imaging or CA-125 testing, even though essential, did not lower this incidence. The upgrade of disease in a further 10 cases along with distant metastases in 2 of these cases also represents a considerable risk of this treatment. There were 2 deaths reported.

FIGURE 5
Forest plot of metaanalysis of live birth rates for fertility-sparing treatment of endometrial cancer



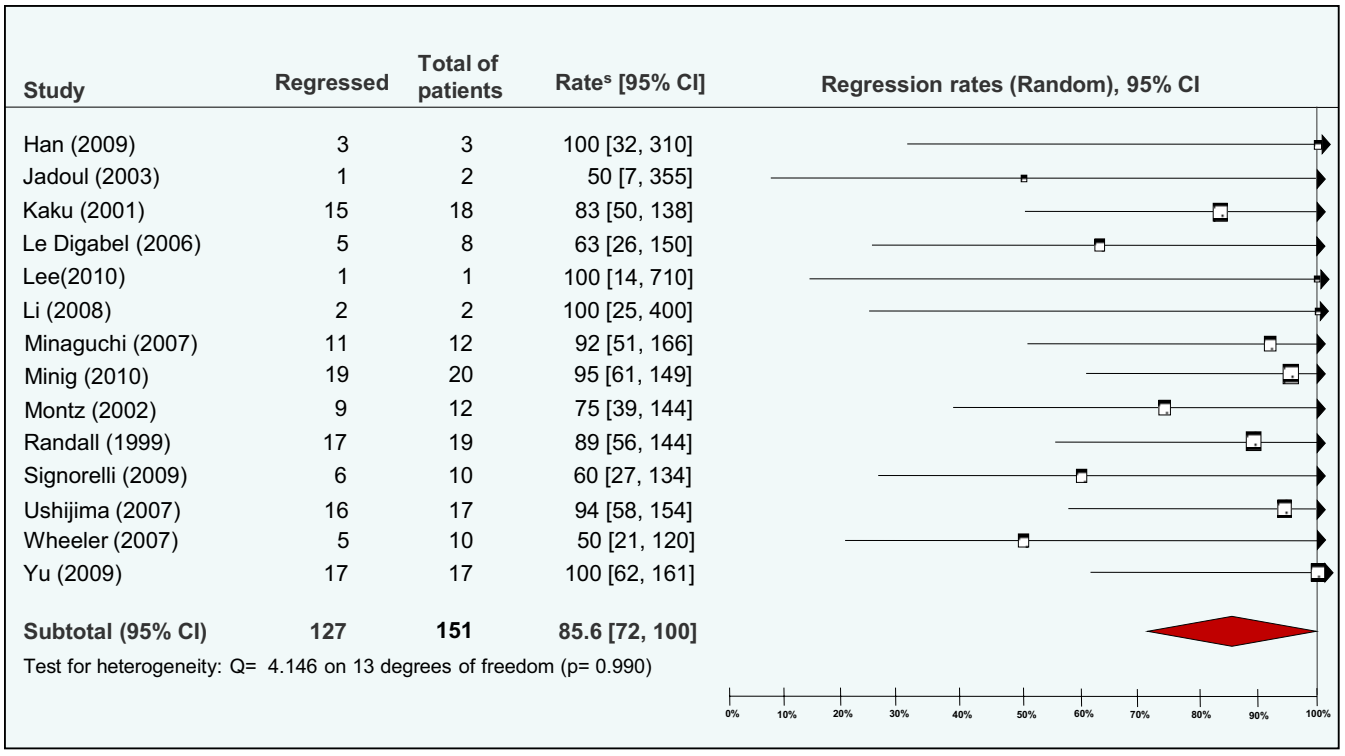
Gallos. Fertility-sparing therapy for endometrial cancer. Am J Obstet Gynecol 2012.

Our study provides an overview of the efficacy of fertility-sparing treatment for early-stage EC and ACH and summarizes the current evidence. It has major clinical relevance for young women who want to preserve their fertility. We reduced potential publication bias by excluding case reports and cases series of fewer than 5 cases. We contacted authors of the primary studies for clarification of relevant information. Finally, we calculated the events of the disease upgrade during follow-up and adverse outcomes with fertility-sparing therapy.

Other systematic reviews produced a mean of the observed rates, which does not take into account the specific weight of the studies and their variability.[44] The use of a random-effects model to combine the data across studies helps to control for differences between the studies. However, because the studies included in this metaanalysis are all observational studies, there is an added layer of potential of bias that is introduced. Hence, the strength of the findings in this review including 34 studies is limited by the dearth of primary literature.[46]

The unstable study estimates and wide confidence intervals because of small numbers along with the risk of bias in most of the studies because of their study design and short-term follow-up reduce the strength of our inferences. Specifically, the relapse and live birth rates may prove to be higher if women were followed up for at least 5 years following their diagnosis.[47] It is reported that relapse may be more likely for obese women,[47] but the primary studies included in our analysis did not report the treatment effects taking into account

FIGURE 6
Forest plot of metaanalysis of relapse rates for fertility-sparing treatment of atypical complex endometrial hyperplasia



Gallos. Fertility-sparing therapy for endometrial cancer. Am J Obstet Gynecol 2012.

obesity. It is also plausible that different types and doses of hormones may have a differential effect on disease regression rates.

We encountered a large clinical variation in fertility-sparing treatment regimens, which prevented us from making comparisons. The variability across the studies was found to be statistically low, but this test may not be a reliable evaluation of the clinical variation in the studies because of small sample sizes. A meta-analysis found that regression is higher with LNG-IUS than oral progestogens for ACH,[3] and it is a popular choice among clinicians in which hysterectomy is not possible.[4]

We believe that even though the diagnosis of EC or ACH in women who want to preserve fertility is uncommon, it is a management dilemma for clinicians. Fertility-sparing treatment does represent an option for these women with encouraging results but also important risks. Women wanting to pursue this treatment would need to be counseled thoroughly about the benefits and the potential risks.

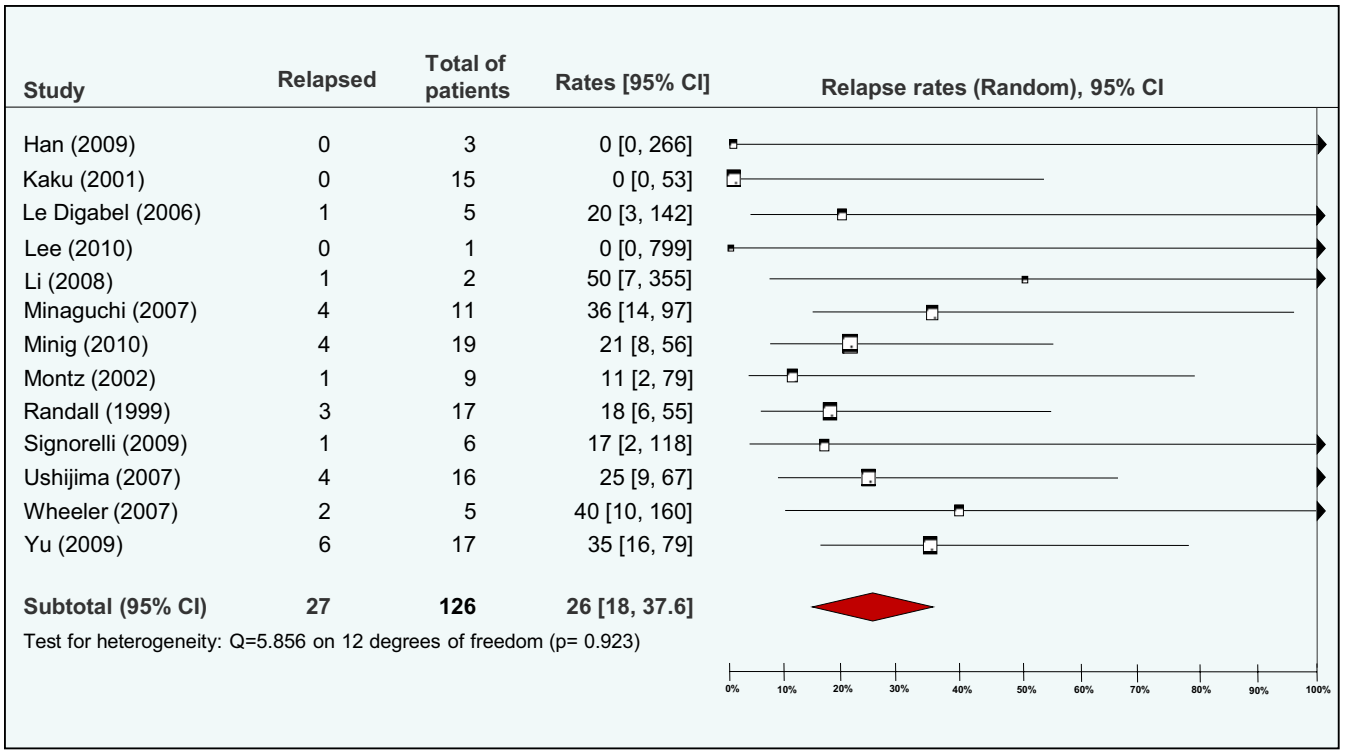
Pretreatment investigations should aim to rule out myometrial invasion and concurrent ovarian cancer, even though there are no reliable tests for this purpose. These should include imaging, such as transvaginal ultrasound and computed tomography or magnetic resonance imaging along with tumor serum markers, but the limitations of these investigations should be taken into account. In the primary studies, these tests did not lower the incidence of ovarian cancer diagnosis during follow-up, but because this is a rare outcome, we may be underpowered to draw conclusions and we also cannot rule out a different case mix across the studies.

We should also point out that there is uncertainty about the treatment regimen and the follow-up, which is reflected in our studies in which various therapies were used. The studies included in this review suggest that when a diagnosis of EC or ACH has been made, this should be treated for at least 3 and up to 12 months. A repeat biopsy should confirm regression before women attempt to get pregnant.

Considering the high relapse rate of the disease once the treatment is stopped and the potential of disease progression, it is sensible to recommend to these women to undergo staging hysterectomy with bilateral salpingo-oophorectomy. This should be recommended to women once their family is complete or if fertility-sparing treatment fails, either because of failure in regressing their disease or relapse. If regression is achieved, we would also recommend that these women be encouraged to undertake assisted reproduction treatment to maximize their chances of a live birth and minimize time before a hysterectomy, which could prevent them from relapse. Immediate assisted reproduction treatment avoids prolonged unopposed estrogen stimulation, which could cause women to relapse.[48]

FIGURE 7

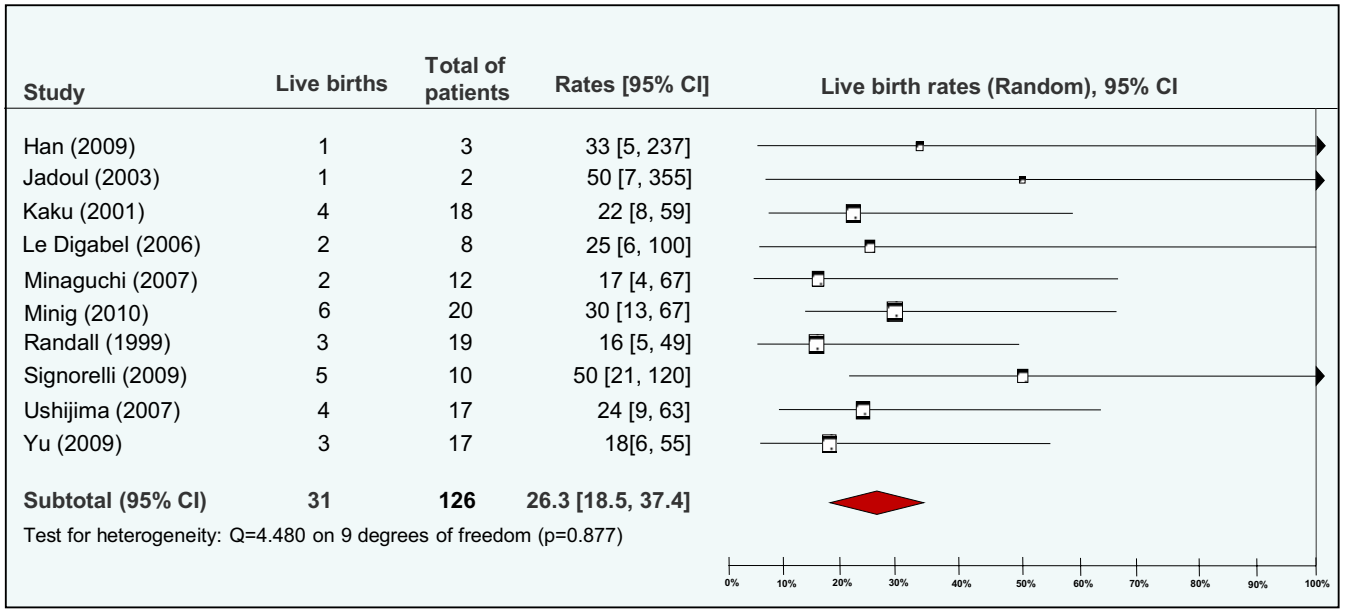
Forest plot of metaanalysis of regression rates for fertility-sparing treatment of atypical complex endometrial hyperplasia



Gallos. Fertility-sparing therapy for endometrial cancer. Am J Obstet Gynecol 2012.

FIGURE 8

Forest plot of metaanalysis of live birth rates for fertility-sparing treatment of atypical complex endometrial hyperplasia



Gallos. Fertility-sparing therapy for endometrial cancer. Am J Obstet Gynecol 2012.

Finally, clinicians should consider following up women who decline hysterectomy for at least 5 years or even longer and not to underestimate the risk of relapse.

In conclusion, this review of observational studies found a high chance of disease regression and encouraging live birth rates of early-stage EC and ACH with fertility-sparing treatment followed by assisted reproduction. The risk of disease relapse and upgrade during follow-up is considerable. Our systematic examination of the published literature confirms that there is only moderate-quality observational evidence to inform clinical practice, and results should be interpreted with caution. Our review should aid the design of prospective, cohort studies to assess the short- and long-term effects of the fertility-sparing treatment. ■

ACKNOWLEDGMENT

We thank Wilma Arnold for her administrative support.

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